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SPECIFIC PRODUCT REVIEWS

Tetanus Toxoid Adsorbed Manufactured by Bureau of Laboratories, Michigan Department of Public Health

1. *Description.* This preparation comprises tetanus toxiod, adsorbed onto aluminum phosphate, and contains 5 to 10 Lf per 0.5 mL.

2. *Labeling*—a. *Recommended use/indications.* This product is recommended for use in the initiation and maintenance of immunity to tetanus in adults. It is specifically recommended that infants and young children be immunized with a combined preparation containing diphtheria toxoid and pertussis vaccine and that adolescent children receive primary immunization with tetanus and diphtheria toxoids of the adult type. The recommended course for primary immunization with this product comprises 2 injections of 0.5 mL intramuscularly 4 to 6 weeks apart, followed by a reinforcing dose 6 to 12 months later. A further reinforcing dose of 0.2 mL every 10 years is advised. The package insert contains no mention of reinforcing doses with injury.

b. *Contraindications.* Acute respiratory or other infections are given as reasons for deferral of immunization, and a warning about the possibility of an unsatisfactory immune response in individuals receiving immunosuppressive drugs is provided. It is stated that individuals not previously immunized will not be protected by tetanus toxoid at the time of injury and recommends instead that tetanus immune globulin and toxoid, given simultaneously at different sites, be given at the time of injury followed by later completion of active immunization against tetanus. A warning about rare anaphylactic responses is included.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* As evidence for efficacy, the general literature regarding the effectiveness of tetanus toxoid is cited in the submission to the Panel (Ref. 1). Also, the current paucity of tetanus in the United States and Michigan, as well, is noted. It is concluded that the absence of tetanus in Michigan is due, at least in part, to the millions of doses of tetanus toxoid distributed from this manufacturer in Michigan during the years 1962 through 1972. Serologic evidence of the immunogenicity of this product includes the results of a study of 81 children who received 3 injections of a preparation containing diphtheria toxoid, pertussis vaccine, and inactivated poliomyelitis vaccine combined with tetanus toxoid. All children achieved satisfactory titers of tetanus antitoxin. Evidence of efficacy of this preparation for reinforcement of immunity against tetanus is provided in a study of 31 individuals, all with a history of prior tetanus immunization, who were given a single 0.2 mL reinforcing dose. All achieved excellent rises in antitoxin titers.

b. *Safety*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* Evidence of human safety is provided by a review of the total number of doses given and the reported reactions over a 10-year period. Among a few million doses there were four reactions resembling immediate anaphylactic shock. The remaining reactions were minor and local.

c. *Benefit/risk ratio.* The benefit-to-risk assessment of this product for primary immunization is probably satisfactory, although the lack of data regarding its efficacy in humans as a primary immunizing agent prevents precise evaluation. Its benefit-to-risk assessement for booster immunization is satisfactory.

4. *Critique.* This extensively used product appears to be quite safe and well-established as efficacious when used for reinforcement of immunity in previously immunized individuals. However, the Panel does not believe that the data relating to the efficacy of tetanus toxoid as a primary immunizing agent when combined with diphtheria toxoid, pertussis vaccine, and poliomyelitis vaccine can be extrapolated to substantiate the efficacy of this product when used without such combination.

5. *Recommendations.* The Panel recommends that this product be placed in Category I as regards its use for booster immunization and that the appropriate license(s) be continued with the stipulation that the labeling should be revised in accordance with currently accepted guidelines and the recommendations of this Report.

The Panel recommends that this product be placed in Category IIIA as regards its use for primary immunization and that the appropriate license be continued for a period not to exceed 3 years during which time the manufacturer shall be expected to develop data regarding the efficacy of this product when used for primary immunization. Labeling revisions are required.

Tetanus Toxiod, Fluid Manufactured by Connaught Laboratories, Limited

1. *Description.* This is a fluid tetanus toxoid containing 12 Lf of toxoid per mL. The toxin is prepared in a casein hydrolysate medium, inactivated by formalin, and diluted in saline containing 15 parts per million of Tween 80.

2. *Labeling*—a. *Recommended use/indications.* The recently revised package insert submitted by the manufacturer contains a satisfactory description of the preparation. For primary immunization, 4 subcutaneous injections of 1 mL are recommended, the first 3 being 4 to 8 weeks apart and the fourth dose 6 to 12 months later. Further reinforcing doses are recommended at 5 year intervals. A reinforcing dose with injury is not recommended if less than 1 year has elapsed since the last dose. If the last administration of tetanus toxoid was more than 5 years previously, both a reinforcing dose and tetanus antitoxin are recommended.

b. *Contraindications.* The manufacturer warns that turbid or cloudy tetanus toxoid should not be used, and a warning about anaphylactic reactions is included. No other contraindication is listed

3. *Analysis*—a. *Efficacy*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* Evidence for efficacy of this product was provided in a 1964–1965 study (Ref. 2) in which 67 children, age 7 to 15 years, were tested for tetanus antibody after a course of 3 injections of

Connaught DT—polio vaccine. Forty-four children had no preimmunization tetanus antibody and were considered primary responders. All of the 44 sera showed a level of 0.125 antitoxin units per mL or greater 1 month after the third injection. Furthermore, an antibody survey in Ontario, where this toxoid is used almost exclusively for tetanus immunization, showed that approximately 98 percent of children less than 18 years of age exhibited satisfactory antibody titers of 0.01 unit per ml of serum or more.

The human efficacy data demonstrate somewhat lower titers following immunization than those achieved with adsorbed preparations.

b. *Safety*—(1) *Animal.* This product meets Federal requriements.

(2) *Human.* of 1,422 injections of tetanus toxoid to employees at Connaught Laboratories, 30 were associated with reactions, all of which were local (Ref. 2). Evidence is also provided by intradermal testing that Sephadex purification of this toxoid markedly reduces local reactions. Only 1 allergic reaction has been reported from several million injections of this toxoid in the last 5 years.

c. *Benefit/risk ratio.* The benefit-to-risk assessment of this product is very satisfactory.

4. *Critique.* This fluid tetanus toxoid has been shown to be both safe and efficacious. Although it is questionable whether any fluid toxoid is as immunogenic as adsorbed preparations, both in terms of antibody titers achieved and duration of immunity, when used as recommended its efficacy considerably exceeds the protective threshold. The package insert deviates from the usual U.S. recommendations for immunization, particularly in the recommendation that tetanus antitoxin be employed along with a booster if more than 5 years has elapsed since the last dose. The use of tetanus antitoxin under these circumstances is superfluous, assuming that primary immunization has been completed. Further, the package insert contains no comment about the effects of immunosuppressive drugs on the immune response to this product.

5. *Recommendations.* Although the Panel feels some preference for absorbed over fluid toxoids, the Panel recommends that this product be placed in Category I and that the appropriate license(s) be continued with the stipulation that the package insert should be revised in accordance with currently accepted guidelines. The package insert should also include a recommendation that for the primary immunization of children a combined product containing diphtheria toxoid and pertussis vaccine, as well as tetanus toxoid, is preferred.

Tetanus Toxoid Manufactured by Cutter Laboratories, Inc.

1. *Description.* Purified tetanus toxoid in sodium chloride, buffered with sodium succinate and containing 1:10,000 thimerosal in a dose of 60 Lf per mL.

2. *Labeling*—a. *Recommended use/indications.* This product is used only for hyperimmunization of adults who volunteer to serve as donors in the preparation of human hyperimmune tetanus globulin. It is administered in a dose of 0.5 mL (30 Lf) given by intramuscular or deep subcutaneous route. It is used only by Cutter Laboratories and not marketed. A donor may receive either no more than 3 injections in a single year followed by a single injection the following year, or no more than 1 booster injection per year for 3 years.

b. *Contraindications.* Any acute respiratory disease or any active infection is reason for deferring an injection. It should be noted here, also, that persons with a history of adverse reactions to tetanus toxoid should be excluded. This is now mentioned under "Adverse Reactions" in the package insert.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* This product meets Federal Requirements.

(2) *Human.* The company summarizes their experience as follows (Ref. 3): Cutter Laboratories, tetanus toxoid, 60 Lf per mL, after total donations of many thousand units of plasma, has been shown to be 90 percent effective in producing adequate plasma tetanus antibody titer (10 International Units or more). Also, after many thousand booster injections and a followup of 22,672 donors, tetanus toxoid, 60 Lf per mL, has been shown to be safe for hyperimmunization of adult plasama donors for plasma used in the production of tetanus immune globulin (human).

b. *Safety*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* Mild side effects were reprted (Ref. 3) a total of 10 times following 22,672 booster injections of tetanus toxoid, 30 Lf, giving a low order of incidence: 0.04 percent. Side effects include five cases of rash and hives, three of mild fever, and one each of swelling of glands and transient dizziness.

c. *Benefit/risk ratio.* This product is designed for hyperimmunization of volunteer subjects. Traditional benefit-to-risk assessment are inappropriate considerations. The risk is low; benefit to mankind is high.

4. *Critique.* This product is used only to produce hyperimmunization of adult tetanus plasma donors. Cutter Laboratories report a very low rate of adverse effects of the relatively high dose of tetanus toxoid (30 Lf) in persons who already have received their basic series of immunization. Prior to the actual booster immunizations each donor reads and signs the tetanus information and donor's consent and release form.

5. *Recommendations.* The Panel recommends that this product be placed in Category I and that the appropriate license(s) be continued with the stipulation that the package insert should be revised in accordance with currently accepted guidelines and recommendations of this Report.

Tetanus Toxoid, Fluid, Manufactured by Dow Chemical Company

1. *Description.* Tetanus toxoid, fluid, is a preparation of tetanus toxoid detoxified with formalin, purified and concentrated by alcohol fractionation, and containing 8 Lf per 0.5 mL human dose. It is preserved with 0.01 percent thimerosal.

2. *Labeling*—a. *Recommended use/indications.* This product is recommended for active immunization against tetanus. The fluid product is recommended primarily for booster use after exposure to tetanus in previously immunized individuals. It is stated that multiple antigen vaccines (i.e., DTP) are preferred for children under 6 years of age.

b. *Contraindications.* Immunization should be deferred if respiratory disease or other active infections exist and in patients under immunosuppressive treatment. Fractional doses are recommended in cerebral injury, asthma, allergies, and histories of severe febrile reactions.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* No data on this specific product were provided.

b. *Safety*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* No specific data on this product were provided. Data from adverse reactions reported to the company and retrieved from their complaint files show no unusual number of reactions. The validity of such data is always open to question, but the rate of reported untoward reactions is somewhat higher with the fluid product than with the adsorbed product. Most of the reactions were local in nature:

allergic or anaphylactoid reactions were noted in a very few cases.

c. *Benefit/risk ratio.* Assuming that the product can be demonstrated efficacious for primary immunizaiton, the benefit-to-risk assessment would be satisfactory, and is satisfactory for booster immunizaiton.

d. *Labeling.* Fluid toxoid is recommended for booster doses following injury in the labeling for both fluid and adsorbed toxoids. The more rapid response to fluid toxoid alluded to is of very dubious significance. The recommendation that boosters be given if the previous dose was received more than 1 year previously is obsolete and encourages excessive booster doses. In addition, fluid toxoid in combination with tetanus immune globulin (TIG) is recommended if more than 10 years have elapsed since the last booster dose. This should be changed to adsorbed toxoid, which is more effectve in combination with TIG. The Public Health Service Advisory Committee on Immunization Practices recommendations on wound management should be followed.

The recommendation to defer immunization when polio is present in the community is also obsolete.

4. *Critique.* In view of the product's ability to meet the potency test in animals specified by minimum requirements, it is adequate for booster immunization use in humans. However, no data are available for the product to demonstrate its efficacy for primary immunization. In addition, in the opinion of some, there is no real need for the fluid product. The alleged superiority of fluid products for booster doses following injury is of dubious significance.

While specific data on reactions were not provided, safety is not considered a significant issue. Complaint file data indicate no unusual or unexpected problems.

5. *Recommendations.* The Panel recommeds that this product be placed in Category I as regards its use for booster immunization and that the appropriate license(s) be continued with the stipulation that the labeling should be revised in accordance with currently accepted guidelines and the recommendations of this Report.

The Panel recommends that this product be placed in Category IIIA as regards its use for primary immunization and that the appropriate license be continued for a period not exceed 3 years during which time the manufacturer shall be expectect to develop data regarding the efficacy of this product when used for primary immunization. Labeling revisions are required.

Tetanus Toxoid Adsorbed Manufactured by Dow Chemical Company

1. *Description.* Tetanus toxoid adsorbed is an alum-precipitated preparation prepared by the same method as the fluid product but containing 12 to 16 Lf per 0.5 mL human dose versus 8 Lf for the fluid product. The adsorbed product contains 2.5 mg alum per dose. It is preserved with 0.01 percent thimerosal.

2. *Labeling*—a. *Recommended use/ indications.* This product is recommended for active immunization against tetanus. The adsorbed product is recommended over the fluid product for primary immunization, although is stated the fluid product may be used. It is stated the multiple antigen vaccines (i.e., DTP) are preferred for children under 6 years of age.

b. *Contraindications.* Immunization should be deferred if respiratory disease or other active infections exist and in patients under immunosuppressive treatment. Fractional doses are recommended in cerebral injury, asthma, allergies, and histories of severe febrile reactions. Cautions are inserted that aluminum adjuvants may cause fat necrosis or draining cysts if not properly injected.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* No data on this specific product were provided.

b. *Safety*—(1). *Animal.* This product meets Federal requirements.

(2). *Human.* No specific data on this product were provided. Data from adverse reactions reported to the company and retrieved from their complaint files show no unusual number of reactions. The validity of such data is always open to question, but the rate of reported untoward reactions is somewhat lower with the adsorbed product than with the fluid product. Most of the reactions were local in nature; allergic or anaphylactoid reactions were noted in a very few cases.

c. *Benefit/risk ratio.* Assuming that the product can be demonstrated efficacious for primary immunization, the benefit-to-risk assessment would be satisfactory, and is satisfactory for booster immunization.

d. *Labeling.* The package insert states that fluid toxoid is recommended for booster doses following injury. The more rapid response to fluid toxoid alluded to is of very dubious significance. The recommendation that boosters be given if the previous dose was received more than 1 year previously is obsolete and encourages excessive booster doses. In addition, fluid toxoid in combinations with tetanus immune globulin (TIG) is recommended if more than 10 years have elapsed since the last booster dose. This should be changed to adsorbed toxoid, which is more effective in combination with TIG. The Public Health Service Advisory Committee on Immunization Practices recommendations on wound management should be followed.

The recommendation to defer immunization when polio is present in the community is also obsolete.

4. *Critique.* In view of the product's ability to meet the potency test in animals specified by minimum requirements, it is adequate for booster immunization use in humans. However, no data are available for the product to demonstrate its efficacy for primary immunization. The alleged superiority of fluid products over adsorbed products for booster doses following injury is of dubious significance.

While specific data on reactions were not provided, safety is not considered to be a significant issue. Complaint file data indicate no unusual or unexpected problems.

5. *Recommendations.* The Panel recommends that this product be placed in Category I as regards its use for booster immunization and that the appropriate license(s) be continued with the stipulation that the labeling should be revised in accordance with currently accepted guidelines and the recommendations of this Report.

The Panel recommends that this product be placed in Category IIIA as regards its use for primary immunization and that the appropriate license be continued for a period not to exceed 3 years during which time the manufacturer shall be expected to develop data regarding the efficacy of this product when used for primary immunization. Labeling revisions are required.

Tetanus Toxoid, Fluid, Manufactured by Eli Lilly and Company

1. *Description.* Each 0.5 mL of this product contains about 7.5 Lf of purified tetanus toxoid in 0.3 M glycine, preserved with 0.01 percent thimerosal.

2. *Labeling*—a. *Recommended use/ indications.* For active immunization against tetanus, four 0.5 mL doses over 1 year are recommended; emergency boosters and active-passive primary immunization are also listed as indications.

b. *Contraindications.* Acute respiratory disease or other active infection are contraindications for use. In individuals who have shown sensitivity reactions to previous injections of tetanus toxoid, a small test dose should be given first. Epinephrine should be available to combat severe systemic reactions if they develop.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* This product meets Federal requirements.

(2). *Human.* No data were presented.

b. *Safety*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* Few complaints for many million doses are reported and suggest that no major problem exists.

c. *Benefit/risk ratio.* There is some reason to question the benefit gained from use of this fluid product for primary immunization in light of the limited available data on efficacy. The benefit-to-risk assessment is satisfactory for booster immunization.

4. *Critique.* This package insert does not point out the general preference for adsorbed rather than fluid toxoid, nor does it indicate the superiority of adsorbed toxoid in active-passive immunization. No data are presented to indicate whether this specific product is effective in man.

5. *Recommendations.* The Panel recommends that this product be placed in Category I as regards its use for booster immunization and that the appropriate license(s) be continued with the stipulation that the labeling should be revised in accordance with currently accepted guidelines and the recommendations of this Report.

The Panel recommends that this product be placed in Category IIIA as regards its use for primary immunization and that the appropriate license be continued for a period not to exceed 3 years during which time the manufacturer shall be expected to develop data regarding the efficacy of this product when used for primary immunization. Labeling revisions are required.

Tetanus Toxoid Adsorbed Manufactured by Eli Lilly and Company

1. *Description.* A sterile suspension of tetanus toxoid precipitated with aluminum potassium sulfate to a final concentration of 2.25 mg per mL (1.125 mg per dose), and suspended in 0.3 M glycine. About 7.5 Lf of toxoid are present per dose; 0.01 percent thimerosal is added as a preservative. The toxoid is purified by the Pillemer process which is said to remove practically all of the inert proteins.

2. *Labeling*—a. *Recommended use/indications.* For active immunization against tetanus, the package insert recommends two 0.5 mL doses 4 to 6 weeks apart and a third dose 1 year later. No special reference is made to the reinforcing dose, but normal booster recommendations are up-to-date.

b. *Contraindications.* Acute respiratory diseases or other active infections are contraindicated. In individuals with preceding history of reactions to tetanus toxoid, small doses should be given. Epinephrine should be at hand.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* No data were presented by the manufacturer. One study by Snyder (Ref. 4) reports rather poor first-dose response to this product, so that some uncertainty exists as to whether it is sufficiently antigenic. It should be noted that this product contained relatively little aluminum ion.

b. *Safety*—(1) *Animal.* this product meets Federal requirements.

(2) *Human.* No controlled observations presented. The complaint file discloses a few complaints for several million doses sold. Most of these were apparently local reactions, pain or febrile reactions. One "systemic" reaction was recorded.

c. *Benefit/risk ratio.* Provided evidence is furnished to indicate that this product is effective for primary immunization, the benefit-to-risk assessment would be satisfactory and is satisfactory for booster immunization.

4. *Critique.* The 1 mL label, included with the manufacturer's submission, is almost unreadable. Other labeling supplied by the manufacturer is clear and informative. Comment(s) on the need for careful resuspension of the precipitate appears in the circular for the prepackaged product but not the standard product. This submission presents less information than is needed on the response of normal individuals to 2 and 3 doses of this product when used as recommended. The labeling should stress the importance of the third dose as part of the primary immunizing series.

5. *Recommendations.* The Panel recommends that this product be placed in Category I as regards its use for booster immunization and that the appropriate license(s) be continued with the stipulation that the labeling should be revised in accordance with currently accepted guidelines and the recommendations of this Report.

The Panel recommends that this product be placed in Category IIIA as regards its use for primary immunization and that the appropriate license be continued for a period not to exceed 3 years during which time the manufacturer shall be expected to develop data regarding the efficacy of this product when used for primary immunization. Labeling revisions are required.

Tetanus Toxoid, Plain, Manufactured by Istituto Sieroterapico Vaccinogeno Toscano "Sclavo"

1. *Description.* This product contains 40 to 50 Lf tetanus toxoid per mL.

2. *Labeling*—a. *Recommended use/indications.* This preparation is recommended for primary immunization for tetanus. The dose is 0.5 mL intramuscularly or subcutaneously in 3 doses 4 to 6 weeks apart for primary immunization and a fourth dose approximately 1 year later. A booster dose every 10 years is recommended. For wound management, a booster dose is not recommended unless more than 5 years have lapsed since the patient's third or last booster dose.

b. *Contraindications.* Immunizations are deferred in any acute or active infection and in persons receiving immunodepressants.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* Claims on efficacy are based on published reports cited in the manufacturer's submission to the Panel (Ref. 5) in which the Sclavo product was used and produced satisfactory antitoxin response. However, published data on efficacy when the product is used for primary immunization are lacking. Separate unpublished data showing antibody response when the adsorbed product is used for primary immunization in children show marginal results, with a relatively large proportion of children not reaching an antitoxin level of 0.01 International Units after 2 injections. The product was proven effective as a booster, however.

b. *Safety*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* The submission states that few complaints of adverse reactions have been reported, without any further analysis of such data.

c. *Benefit/risk ratio.* The benefit-to-risk assessment would be satisfactory for primary immunization if the product is shown to be effective and is satisfactory for booster immunization.

d. *Labeling.* Instructions regarding booster doses following wounds could be improved by including the table from the Public Health Service Advisory Committee on Immunization Practices recommendations.

4. *Critique.* This product meets the U.S. standards for animal safety and

potency and appears to be safe in humans. Additional serologic data establishing its efficacy for use in primary immunization are needed. The efficacy of the product as a booster is established. In the package insert, recommendations regarding booster doses should follow U.S. guideines.

Possibility and description of adverse reactions should be mentioned. The manufacturer's data submission does not describe or elaborate on reported adverse reactions.

5. *Recommendations.* The Panel recommends that this product be placed in Category I as regards its use for booster immunization and that the appropriate license(s) be continued with the stipulation that the labeling should be revised in accordance with currently accepted guidelines and the recommendations of this Report.

The Panel recommends that this product be placed in Category IIIA as regards its use for primary immunization and that the appropriate license be continued for a period not to exceed 3 years during which time the manufacturer shall be expected to develop data regarding the efficacy of this product when used for primary immunization. Labeling revisions are required.

Tetanus Toxoid Adsorbed Manufactured by Istituto Sieroterapico Vaccinogeno Toscano "Sclavo"

1. *Description.* This product contains 10 Lf tetanus toxoid and 2 mg [1] aluminum hydroxide per 0.5 mL dose. According to the package insert, this product is highly purified, but methods of production and purification are not described.

2. *Labeling*—a. *Recommended use/indications.* This preparation is recommended for primary immunization for tetanus. The dose is 0.5 mL intramuscularly in 2 doses 6 to 8 weeks apart for primary immunization and a third dose approximately 1 year later. A booster dose every 10 years is recommended. For wound management, a booster dose is not recommended unless more than 5 years have elapsed since the patient's third or last booster dose.

b. *Contraindications.* Immunizations are deferred in any acute or active infection and in persons receiving immunodepressants.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* This product meets Federal requirements.

[1]The labeling submitted to the advisory Panel is wrong. This product contains 1 mg of $Al(OH)_3$ per dose. It is the Panel's understanding that the labeling has been corrected.

(2) *Human.* Claims of efficacy are based on published reports cited in the manufacturer's submission to the Panel (Ref. 6) in which the Sclavo product was used in special clinical settings and produced satisfactory antitoxin responses. However, published data on efficacy when the product is used for primary immunization are lacking. Separate unpublished data showing antibody response when the adsorbed tetanus toxoid was used for primary immunization in Italian children showed marginal results, with a relatively large proportion of children not reaching an antitoxin level of 0.01 International Unit after 2 injections. The product was proved effective as a booster, however.

In 1977, completed studies of this manufacturer's DT and Td among children and adults, conducted in Mexico, show satisfactory antitoxin response for tetanus as well as diphtheria. These studies were included in the manufacturer's license application to FDA.

b. *Safety*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* The submission states that few complaints of adverse reactions have been obtained, without any further analysis of such data.

c. *Benefit/risk ratio.* The benefit-to-risk assessment of this product is satisfactory.

d. *Labeling.* Instructions regarding booster doses following wounds could be improved by including the table from the Public Health Service Advisory Committee on Immunization Practices recommendations.

4. *Critique.* This product meets the U.S. standards for animal safety and potency and appears to be safe in humans. Additional data were provided to the Panel subsequent to the original submission. The data were submitted in support of DT and Td products, but in accordance with the guidelines established by the Panel regarding the extrapolation of data from the use of combined vaccines, there was sufficient information to show that this product is safe and effective. In the package insert, recommendations regarding booster doses should follow the U.S. guidelines.

The possibility and description of adverse reactions should be included in the package insert. The manufacturer's data submission does not describe or elaborate on reported adverse reactions.

5. *Recommendations.* The Panel recommends that this product be placed in Category I and that the appropriate license(s) be continued because there is substantial evidence of safety and effectiveness for this product. Labeling should be revised in accordance with currently accepted guidelines and the recommendations of this Report.

Tetanus Toxoid Manufactured by Lederle Laboratories Division, American Cyanamid Co.

1. *Description.* This product is a fluid tetanus toxoid prepared from toxin produced by the method of Mueller and Miller, detoxified with formaldehyde, "refined" by the Pillemer method, diluted in phosphate buffer and 0.3 M glycine to a final concentration of 5 Lf per dose, and preserved with 0.1 percent thimerosal.

2. *Labeling*—a. *Recommended use/indications.* For active immunization against tetanus, the dose is three 0.5 mL injections intramuscularly at 3 to 4 week intervals and a fourth dose 1 year later. The labeling notes the immunogenic superiority of adsorbed toxoids and the lack of any significant advantage of fluid toxoid as regards speed of booster response. Wound booster recommendations appear to be based on current Public Health Service Advisory Committee on Immunization Practices recommendations.

b. *Contraindications.* Acute respiratory disease or other active infection; immunosuppressive or cytotoxic therapy.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* Reports of the Investigational New Drug 262 study included in the manufacturer's submission to the Panel (Ref. 7) suggest very poor primary response to preparation D (a fluid toxoid containing 6 Lf per dose but described as "the current commercial product"). Of 10 subjects, 2 were "protected," 4 had minimal antibody levels, and 3 had no measurable response. In a second study, only 2 of 6 subjects given this toxoid were primary responders; both of them had only marginal protection at 90 days. The protocol fails to state whether a third injection of the fluid toxoid was given, however, and then antibody responses suggest that it was not given.

b. *Safety*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* Twenty-eight minor complaints and apparently no major ones in 3 years are recorded, with several million doses distributed. This suggests a low degree of reactivity. Reactions in the studies noted above were nil (in six subjects).

c. *Benefit/risk ratio.* The benefit-to-risk assessment of this product would be satisfactory if the product is shown to be affective for primary immunization